Support for the amendment to claim 1 is found in the specification at page 13, lines 6-11; in Examples 2-3; and in Figures 1-3.

Claim 23 is amended to recite proper antecedent basis.

The 35 U.S.C. § 102(e) Rejection

The Examiner rejected claims 4, 6-10, 13 and 23-24 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,197,789 (Grainger *et al.*). Claims 4, 13 and 24 have been cancelled, rendering the rejection to claims 4, 13 and 24 moot. Claim 23, upon which claims 6-10 depend, has been amended to no longer be dependent upon claim 4, thus overcoming this rejection of claim 23 and of claims 6-10. Withdrawal of the 35 U.S.C. § 102(e) rejection is respectfully requested.

The 35 U.S.C. § 103(a) Rejection

The Examiner rejected claims 1, 3, 11 and 22 under 35 U.S.C. § 103(a) as being unpatentable over Grainger *et al.* According to the Examiner, Grainger *et al.* teach that Applicant's active agent is useful to inhibit endothelial cell activation (page 4 of the Office Action). Therefore, the Examiner alleges that the art worker would be "motivated to employ Applicant's active agent to reduce or inhibit any activation of endothelium." Regarding claim 11, the Examiner asserts that the art worker would be motivated to incorporate agents useful for treating diabetes, hypertension and coronary artery disease with the active agents of Grainger *et al.* to achieve at least an additive effect (pages 5-6 of the Office Action). Claims 3 and 22 have been cancelled, rendering this rejection to claims 3 and 22 moot. As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

As amended, claim 1 is directed to a method to normalize the contractile response of an endothelially-compromised vascular smooth muscle cell to a vasoconstrictor agonist in a patient in need of such normalization, comprising administering a pharmaceutically effective amount of a CLC3 blocker, or a pharmaceutically acceptable salt thereof. Claim 11 is directed to such a method, further comprising administering a pharmaceutically-effective compound selected from

the group consisting of an anti-diabetes agent, an anti-hypertension agent, an anti-coronary artery disease agent, and an anti-restenosis agent.

Grainger *et al.* disclose a therapeutic method for preventing or treating a cardiovascular or vascular indication characterized by a decreased lumen diameter, wherein a therapeutic agent that elevates the level of TGF-beta is employed (column 2, line 37 to column 3, line 2 and column 10, lines 44-46). Grainger *et al.* disclose that such an agent can inhibit the activity of a vascular smooth muscle cell (VSMC), such as proliferation, contraction, and migration (column 17, lines 41-48), as well as inhibit the "pathological" or "abnormal" activity of VSMC (column 3, lines 17-22 and column 6, lines 15-16), defined by Grainger *et al.* as "division, growth or migration of cells occurring more rapidly or to a significantly greater extent than typically occurs in a normally functioning cell of the same type, or in lesions not found in healthy tissues" (column 7, lines 61-65). However, there is nothing in Grainger *et al.* that teaches or suggests normalizing the contractile response of an endothelially-compromised vascular smooth muscle cell to at least one vasoconstrictor agonist.

The Examiner is urged to consider that the "inhibition" of VSMC activity is not the equivalent of smooth muscle cell "normalization." Applicant submits that a "new use" of a composition is clearly patentable subject matter under 35 U.S.C. § 100(b). The present claims are directed to previously unknown uses for CLC3 blockers, *e.g.*, tamoxifen, which are based on the discovery that, *inter alia*, tamoxifen normalizes the increased sensitivity to vasoconstrictor agonists that is associated with endothelially-compromised smooth muscle, *i.e.*, smooth muscle having a damaged or disrupted endothelial layer. To render such a claim obvious, the obviousness of the claimed result must be apparent to one of skill in the art from the prior art, viewed without the benefit of knowledge of Applicant's invention. Thus, even if tamoxifen has been reported to "inhibit" vascular smooth muscle cell contraction, there is nothing in the cited art to suggest that it can correct or normalize the effect of vasoconstrictor agonists on endothelially-compromised VSMC. Therefore, Grainger *et al.* do not obviate the pending claims, and Applicant respectfully requests that the 35 U.S.C. § 103(a) rejection be withdrawn.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612 373-6961) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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The undersigned hereby certifies that this correspondence is being transmitted by facsimile (FAX NO. 703-308-7924) to: Box AF, Commissioner of Patents, Attn.: Examiner Jennifer Kim, GAU 1617, Washington, D.C. 20231, on this 23 day of January, 2003.

Candis B. Buending
Name

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Signature